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PATENTS
Attorney Docket No. 10008-1191

CERTIFICATE OF MAILING

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Derek P. Freyberg, Reg. No. 29,250 — 7/14/03 Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Steven Y. Ng et al.		: Confirmation No.:	7251
App. No.:	09/854,435	: Art Unit:	1711
Filed:	May 11, 2001	: Examiner:	Samuel A. Acquah
For:	Bioerodible polyorthoesters containing hydrogen bonding groups		

Mailstop Appeal Brief – Patents
Commissioner for Patents
PO Box 1450
Alexandria VA 22313-1450

Sir:

TRANSMITTAL

Transmitted herewith is an Appeal Brief, in triplicate.

The Appeal Brief filing fee of $320 is enclosed by check. Please charge any fees that may be required, or credit any refund, to Deposit Account No. 08-1641, referring to 10008-1191. A duplicate of this document is enclosed.

Respectfully submitted,

Derek P. Freyberg
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July 14, 2003

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Sir:

APPEAL BRIEF

On May 22, 2003, Appellants filed a Notice of Appeal from the Final Rejection dated February 26, 2003, rejecting claims 1 – 14 and 17 – 19, and this Notice of Appeal was received on May 28, 2003 [OIPE date stamp on return receipt postcard].

The following constitutes Appellants' Brief on Appeal.

(1) Real party in interest

The real party in interest is AP Pharma, Inc., as assignee of the inventors, Steven Y. Ng and Jorge Heller, by an assignment recorded on August 13, 2001 at Reel 012079, Frame 0956.

(2) Related appeals and interferences

There are no related appeals or interferences.

(3) Status of claims

Claims 1 – 14 and 17 – 35 are pending in this application.

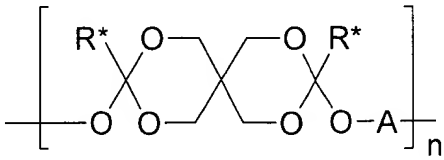
Claims 20 – 35 stand withdrawn from consideration (oral restriction requirement of September 25, 2002); claims 1 – 14 and 17 – 19 stand rejected, and the rejection of claims 1 – 14 and 17 – 19 is appealed.

(4) Status of amendments

No amendment has been filed subsequent to the final rejection.

(5) Summary of the invention

The invention of rejected claims 1 – 14 is polyorthoesters of the formula:



that are a combination of two or more of four types of units (a "unit" being an individual segment of the polyorthoester chain, consisting of the residue of a diketene acetal molecule and the residue of a polyol – *see* the definition at page 9, lines 3 and 4, of the specification): "α-hydroxy acid containing" units, where A is R^1 – *see* the definition at page 9, lines 5 – 7, of the specification; "hard" units, where A is R^2 – *see* the definition at page 9, line 11, of the specification; "soft" units, where A is R^3 – *see* the definition at page 9, lines 11 – 12, of the specification; and "hydrogen bonding" units, where A is R^4 – *see* the definition at page 9, line 12, of the specification. The presence of "α-hydroxy acid containing" units and "hydrogen bonding" units in the polyorthoester is required in at least 0.1 mol% – see page 11, line 10, of the specification; the presence of "hard" units and "soft" units is optional.

The invention of rejected claims 17 – 19 is processes for the preparation of such polyorthoesters; with claim 17 being a claim to a process for preparing the polyorthoester of claim 1, claim 18 being more general in being a claim to the reaction product of a diketene acetal and a mixture of polyols [the claim, in the first line of subpart (b), says "a polyol or a mixture of polyols", but the requirement in the body of subpart (b) is for at least two kinds of polyols], and claim 19, dependent on claim 18, including the requirement that at least one polyol have more than two hydroxy functional groups.

The physical properties of the polyorthoesters are determined by the content of the various units, with an increasing content of "hard" and "hydrogen bonding" units resulting in a more solid polyorthoester and an increasing content of "soft" units resulting in a more liquid or ointment-like polyorthoester – *see* the discussion at page 12, line 25 – page 13, line 3, of the specification. An increasing content of "α-hydroxy acid containing" units results in a polyorthoester having a higher rate of bioerodibility – *see* the discussion at page 11, lines 15 – 25, of the specification. Thus, by variation of the content of the various units, polyorthoesters of controlled physical state and bioerodibility may be prepared.

The polyorthoesters are described at page 9, line 19 – page 13, line 19, of the specification, with a definition of the polyorthoesters of the same scope as claim 1 at page 9, line 21 – page 11, line 10. The process for their preparation (including the preparation of starting materials) is described at page 13, line 21 – page 18, line 17, of the specification and by reference to certain patents and non-patent documents incorporated into the specification by reference, with a definition of the process of the same scope as claims 17 and 18 (except for the percentage compositional limitations) at page 13, line 24 – page 14, line 2, and a discussion of the use of polyols having more than two hydroxy functional groups at page 14, lines 14 – 29.

(6) Issue

Whether claims 1 – 14 and 17 – 19 are rejectable under 35 USC 103(a) as being unpatentable over Heller et al., US Patent No. 5,968,543 ("**Heller et al.**") combined with Sparer et al., US Patent No. 4,549,010 ("**Sparer et al.**").

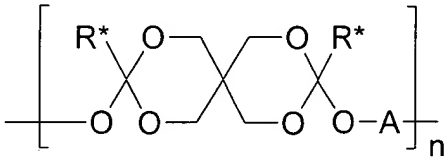
(7) Grouping of claims

Appellants will argue the patentability of claims 1 – 14 and 17 – 19 together.

(8) Argument

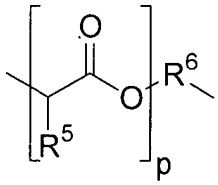
Claims 1 – 14 and 17 – 19 are not unpatentable over Heller et al. combined with Sparer et al.

Heller et al. discloses poly(ortho esters) of the formula:



(I)

(the formula from the patent has been modified to match that of the present application, without change in substance)
where the A groups represent the residues of diols, at least 0.1% of which must be diols of the formula:



i.e. diols based on α-hydroxy acids; the remaining diol(s) being classified as "hard" or "soft" depending on the rigidity of the diol and being based on hydrocarbons (being diols such as 1,4-cyclohexane-dimethanol, hydroquinone, 1,10-decanediol, and the like) or on such oxygen-containing units as polyethylene glycol, or on alkylene acetals.

The poly(ortho esters) are said to be useful as orthopedic implants and as vehicles for the sustained delivery of pharmaceutical, cosmetic, and agricultural agents; where the rate and degree of the hydrolysis of the poly(ortho esters), and hence the release of an active ingredient, may be controlled without the addition of exogenous acid by the presence of these α-hydroxy acid-containing diols within the polymer.

They are prepared by the copolymerization of a diketene diacetal with a mixture of diols, the mixture including at least 0.1% of an α-hydroxy acid-containing diol (see, for example, Example 3(a), column 16, lines 44 - 64). Thus the poly(ortho esters) are random copolymers consisting of randomly alternating poly(ortho ester) units based on the diketene diacetal and one of the up to three different types of diols.

Sparer et al. discloses poly(ortho ester) thermoplastic elastomers prepared from:
(A) a diketene diacetal;
(B) a long-chain non-polar flexible diol (diols containing one or more of an amide, urethane, urea, or imide group); and
(c) a diol selected from (i) diols containing at least one functional group which produces hydrogen bonding or other association, and (ii) rigid symmetrical diols.

The poly(ortho esters) are preferably block copolymers, containing "soft" or flexible segments (based on the diketene diacetal and the flexible diols) and "hard" or rigid segments (based on the diketene acetal and the rigid diols (the functional-group containing diols and/or the rigid symmetrical diols)). The soft segments are stated to confer a high degree of extensibility to the block copolymer, while the hard segments are stated to act through interchain interactions to tie adjacent polymer chains through a "physical crosslink". Thus the block copolymers are stated to form thermoplastic elastomers.

In a preferred preparation, the poly(ortho ester) segments based on the flexible diols are prepared separately from poly(ortho ester) segments based on the rigid diols; although it is stated that the poly(ortho esters) may be prepared by random copolymerization. Each of the examples discloses only the preparation of a block copolymer, where a "soft" segment is prepared by the reaction of the diketene diacetal and a flexible diol, after which the "hard" segment is added by the addition of further diketene diacetal and a "hard" diol and continued polymerization.

Discussion

In the final rejection, the Examiner stated:
"As indicated in the previous action, the primary reference (**Heller et al.**) discloses polymers with controlled physical state and bioerodibility such that the rate and degree to which they are hydrolyzed can be controlled by incorporating esters of short-chain alpha-hydroxy acids. This prior art does not disclose the use of diols which provide hydrogen bonding, comprising amide, urethane, urea, and imide groups. However, the secondary reference (**Sparer et al.**) discloses bioerodible poly(ortho ester) derived from a diketene acetal and long-chain flexible diol as well as a diol which provides hydrogen bonding as indicated above. The secondary reference clearly teaches that by incorporating the diols as indicated above, there is provided a random or copolymer with predictable erodibility. Thus it is the Examiner's position that the preparation of a bioerodible polypolyorthoesters containing hydrogen bonding groups such as claimed, and prepared from a diketene acetal and mixtures of diols as claimed would have been prima facie obvious, based on a combination of the teachings of the cited prior arts as explained supra."

Appellants respectfully disagree, for they contend that the Examiner has failed to establish a *prima facie* case of obviousness.

MPEP 2142 states:
"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). ...
The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)."

Then, with regard to suggestion or motivation to modify the reference, MPEP 2143.01 states

""In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992)."

The Examiner's statements that "the preparation of a bioerodible polypolyorthoesters containing hydrogen bonding groups such as claimed, and prepared from a diketene acetal and mixtures of diols as claimed would have been prima facie obvious, based on a combination of the teachings of the cited prior arts as explained supra" is not to the contrary, because Appellants submit that these statements do not set out the proper standard for the establishment of *prima facie* obviousness, which standard is described in the MPEP excerpts and cases cited above.

It is beyond doubt that **Heller et al.** does not disclose a poly(ortho ester) based on a diol containing an amide, urethane, urea, or imide group; and Appellants submit that it is equally clear that there is no suggestion in **Heller et al.** of such a poly(ortho ester). Similarly, it is beyond doubt that **Sparer et al.** does not disclose a poly(ortho ester) based on a diol containing an α-hydroxy acid; and Appellants submit that it is equally clear that there is no suggestion in **Sparer et al.** of such a poly(ortho ester).

Moreover, while **Sparer et al.** does permit random copolymerization, it is also clear that for **Sparer et al.** to achieve the stated goal of providing a thermoplastic elastomer, the poly(ortho ester) can not be a random copolymer but must be a block copolymer, for it is the alternating hard and soft segments that make the polymer both thermoplastic (as groups of hard segments lose their interchain crystallinity and bonding) and elastomeric (from the presence of the soft segments, not merely soft units). Thus Appellants submit that a person of ordinary skill in the art would understand **Heller et al.** to be directed to a random copolymer and **Sparer et al.** to be directed to a block copolymer, and would not look to **Sparer et al.** to modify **Heller et al.**

For the establishment of *prima facie* obviousness, then, the Examiner must provide some teaching, suggestion, and motivation for the combination of **Heller et al.** and **Sparer et al**. to achieve the poly(ortho ester) and its method of preparation as claimed. This the Examiner has not done: the rejection merely asserts obviousness, and no reasoning has been given as to why a person of ordinary skill in the art would seek to modify the poly(ortho ester) of **Heller et al.** by including in that poly(ortho ester) a diol containing an amide, urethane, urea, or imide group as found in **Sparer et al.**. It is not sufficient that the modification could be made, or even that to do so would be within the skill of the art (which is not admitted), case law (*for example, Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)) makes it clear that the level of skill in the art cannot be relied upon to provide motivation.

For the reasons given above, Appellants submit that claims 1 – 14 and 17 – 19 are not unpatentable over **Heller et al.** combined with **Sparer et al.** Reversal of the rejection is respectfully requested.

Respectfully submitted,

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July 14, 2003

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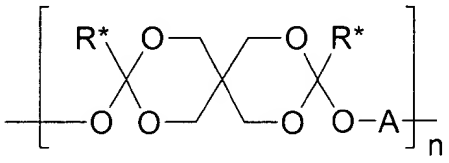
(9) Appendix

Claims 1 – 14 and 17 – 19, the claims involved in the appeal, are as follows:

1. A polyorthoester of formula I:



(I)

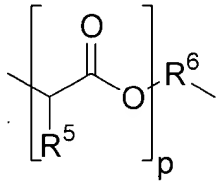
where:

R* is a C_{1-4} alkyl;

n is an integer of at least 5; and

A is R^1, R^2, R^3, or R^4, where

R^1 is:

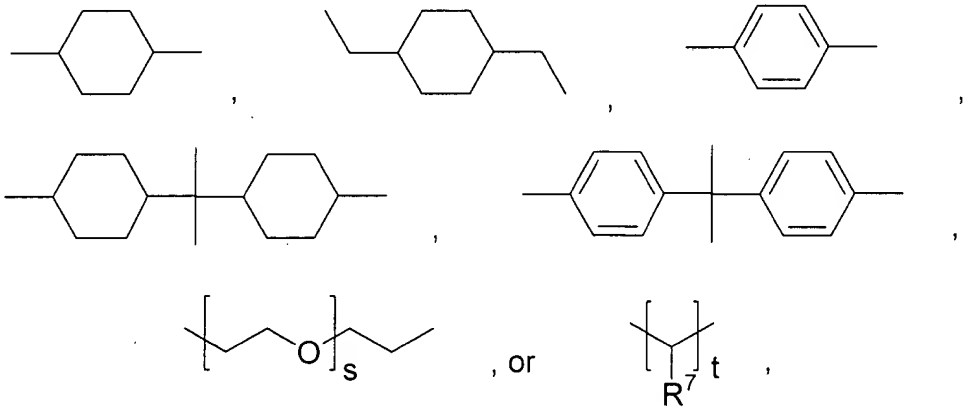


where:

p is an integer of 1 to 20;

R^5 is hydrogen or C_{1-4} alkyl; and

R^6 is:



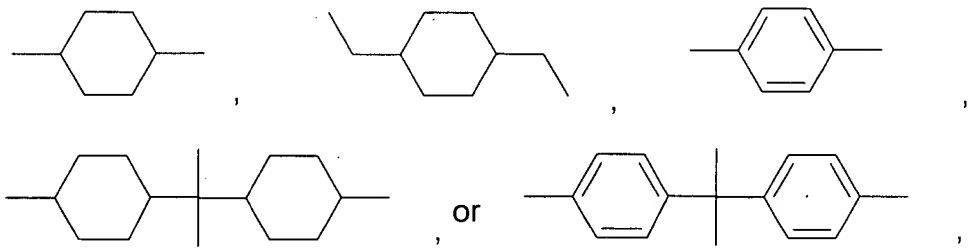
where:

s is an integer of 0 to 30;

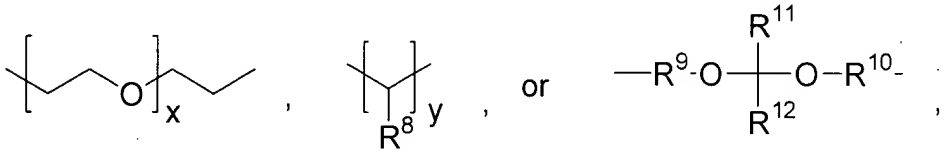
t is an integer of 2 to 200; and

R^7 is hydrogen or C_{1-4} alkyl;

R^2 is:



R^3 is:



where:

x is an integer of 0 to 30;

y is an integer of 2 to 200;

R^8 is hydrogen or C_{1-4} alkyl;

R^9 and R^{10} are independently C_{1-12} alkylene;

R^{11} is hydrogen or C_{1-6} alkyl and R^{12} is C_{1-6} alkyl; or R^{11} and R^{12} together are C_{3-10} alkylene; and

R^4 is a diol containing at least one functional group independently selected from the group consisting of amide, imide, urea, and urethane groups;

in which at least 0.1 mol% of the A units are R^1, and at least 0.1 mol% of the A units are R^4.

2. The polyorthoester of Claim 1 where n is about 5 to about 1000.

3. The polyorthoester of Claim 2 where n is about 20 to about 500.

4. The polyorthoester of Claim 3 where n is about 30 to about 300.

5. The polyorthoester of Claim 1 which comprises about 1 to about 50 mole percent of units in which A is R^1.

6. The polyorthoester of Claim 5 which comprises about 2 to about 30 mole percent of units in which A is R^1.

7. The polyorthoester of Claim 6 which comprises about 5 to about 30 mole percent of units in which A is R^1.

8. The polyorthoester of Claim 7 which comprises about 10 to about 30 mole percent of units in which A is R^1.

9. The polyorthoester of Claim 1 where p is 1 to 6.

10. The polyorthoester of Claim 9 where p is 1 to 4.

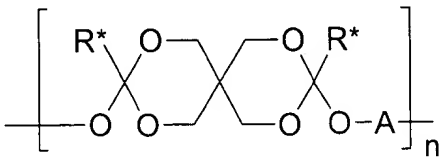
11. The polyorthoester of Claim 10 where p is 1 to 2.

12. The polyorthoester of Claim 1 where R^5 is hydrogen or methyl.

13. The polyorthoester of Claim 1 which comprises up to about 20 mole percent of units in which A is R^2.

14. The polyorthoester of Claim 1 which comprises about 60 to about 99.9 mole percent of units in which A is R^2.

17. A process of preparing a polyorthoester of formula I:



(I)

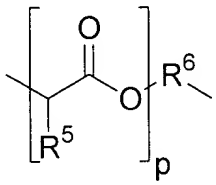
where:

R* is a C_{1-4} alkyl;

n is an integer of at least 5; and

A is R^1, R^2, R^3, or R^4, where

R^1 is:

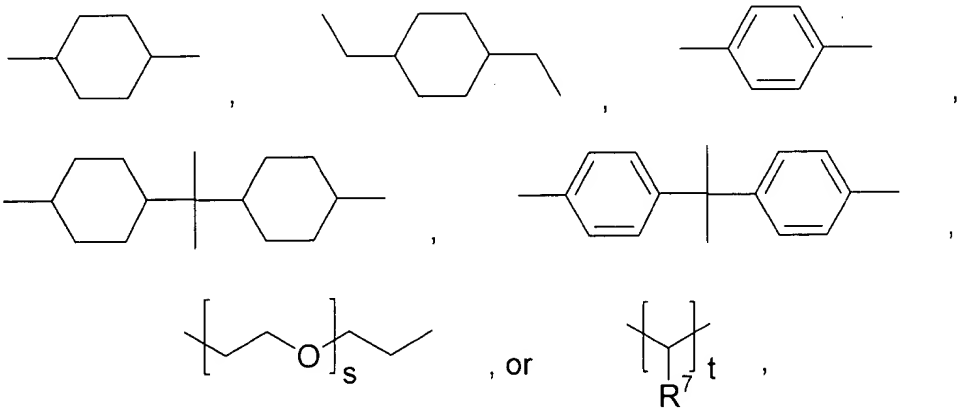


where:

p is an integer of 1 to 20;

R^5 is hydrogen or C_{1-4} alkyl; and

R^6 is:



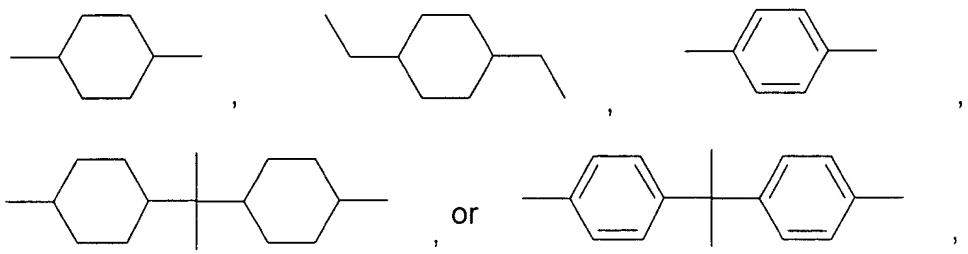
where:

s is an integer of 0 to 30;

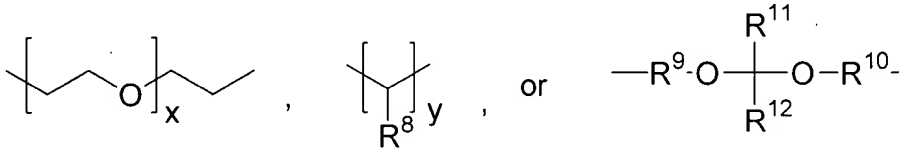
t is an integer of 2 to 200; and

R^7 is hydrogen or C_{1-4} alkyl;

R^2 is:



R^3 is:



where:

x is an integer of 0 to 30;

y is an integer of 2 to 200;

R^8 is hydrogen or C_{1-4} alkyl;

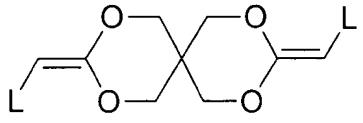
R^9 and R^{10} are independently C_{1-12} alkylene;

R^{11} is hydrogen or C_{1-6} alkyl and R^{12} is C_{1-6} alkyl; or R^{11} and R^{12} together are C_{3-10} alkylene; and

R^4 is a diol containing at least one functional group independently selected from the group consisting of amide, imide, urea, and urethane groups;

in which at least 0.1 mol% of the A units are R^1, and at least 0.1 mol% of the A units are R^4,

the process comprising reacting a diketene acetal of formula II:



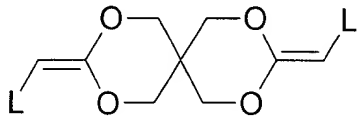
(II)

where L is hydrogen or a C_{1-3} alkyl,

with a diol of the formula HO-R^1-OH and a diol of the formula HO-R^4-OH, and optionally at least one diol of the formulae HO-R^2-OH and HO-R^3-OH.

18. A polyorthoester that is the product of a reaction between:

(a) a diketene acetal of formula II:

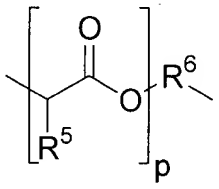


(II)

where L is hydrogen or a C_{1-3} alkyl, and

(b) a polyol or mixture of polyols in which at least 0.1 mole percent of the total polyol content is a diol of the formula HO-R^1-OH, where

R^1 is:

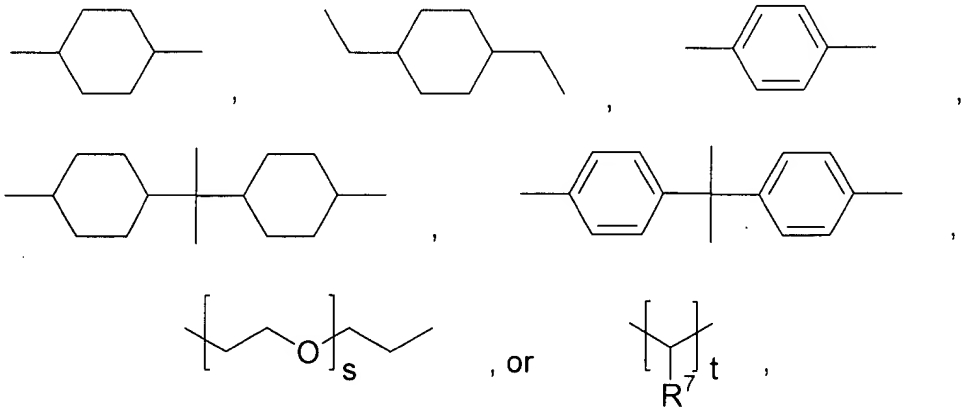


where:

p is an integer of 1 to 20;

R^5 is hydrogen or C_{1-4} alkyl; and

R^6 is:



where:

s is an integer of 0 to 30;

t is an integer of 2 to 200; and

R^7 is hydrogen or C_{1-4} alkyl;

R^{11} is hydrogen or C_{1-6} alkyl and R^{12} is C_{1-6} alkyl; or R^{11} and R^{12} together are C_{3-10} alkylene; and

at least 0.1 mole percent of the total polyol content is a diol of the formula HO-R^4-OH, where R^4 is the residue of a diol containing at least one functional group independently selected from the group consisting of amide, imide, urea, and urethane groups.

19. The polyorthoester of Claim 18 where at least one of the polyols is a polyol having more than two hydroxy functional groups.